



Comparison of the long-term efficacy of 3- and 5-year house dust mite allergen immunotherapy

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ABSTRACT

Background: The recommended duration of specific immunotherapy (SIT) treatment relies on empiric data and is not well documented.

Objective: To detect possible differences in the long-term effectiveness between 3 and 5 years of house dust mite (HDM) SIT in asthmatic children.

Methods: We performed a 3-year natural history study of 90 asthmatic children who were sensitive only to HDM. Three groups were recruited: 30 who had completed 3 years of HDM SIT (SIT3), 30 who had completed 5 years of HDM SIT (SIT5), and 30 who had an indication for HDM SIT but whose parents refused HDM SIT. Patients attended an enrollment visit in 2007, after SIT discontinuation, and 3 annual follow-up visits at the clinic. The long-term effectiveness of HDM SIT was primarily assessed via analysis of the reduction in required inhaled corticosteroid dose, forced expiratory volume in 1 second, and asthma remission.

Results: A total of 84 children completed the study. Both SIT durations produced excellent results; asthma remission in both SIT3 (50%) and SIT5 (54%) groups was significantly higher when compared with control (3.3%). The minimal controlling inhaled corticosteroid dose reduction in SIT5 group (median, 75%) was significantly higher compared with the SIT3 group (median, 50%) after immunotherapy discontinuation; after 3 years without SIT, no differences were found between the SIT5 and SIT3 groups (median, 100% and 94%, respectively). We observed a slightly higher increase in forced expiratory volume in 1 second in the SIT5 group compared with the SIT3 group.

Conclusion: Three years of SIT is an adequate duration for the treatment of childhood asthma associated with HDM allergy because 2 further years of SIT added no clinical benefit.

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Introduction

Allergen specific immunotherapy (SIT) is the only treatment of allergy modifying the immune response.^{1,2} Immunotherapy alleviates the symptoms, prevents the onset of new sensitizations, and reduces the risk of developing asthma. Moreover, its clinical efficacy lasts many years.³

An adequate SIT treatment should ideally produce a long-term therapeutic benefit after its completion. The results obtained in some trials suggest that the duration of the treatment might influence the duration of the clinical effect after completion of SIT.^{4–6} The recommended duration of SIT treatment relies on empiric data and is not well documented. To our knowledge, there are only 2 trials that prospectively explore the currently recommended dura-

tion limits of SIT,^{7,8} but the long-term efficacy of SIT was not assessed in these studies. However, no publications have compared how the duration of SIT might influence the long-term efficacy of immunotherapy.

Our objective was to compare the long-term efficacy of 3 and 5 years of house dust mite (HDM) SIT in children with asthma. Efficacy was assessed on the basis of a steroid-sparing effect, asthma symptoms score, lung function, asthma remission, methacholine challenge, and the Paediatric Asthma Quality of Life Questionnaire (PAQLQ).

Methods

Patients

Ninety boys and girls with IgE-dependent asthma caused by sensitization only to HDMs (*Dermatophagoides farinae* [n = 5] or *Dermatophagoides pteronyssinus* [n = 7] or both [n = 78]) were randomly selected (computer-generated allocation schedule) from an outpatient population at our allergy clinic center who fulfilled the inclusion criteria (n = 180 potential study candidates). We

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included patients who completed a 3-year course of SIT (SIT3 group, $n = 30$), those who completed a 5-year course of SIT (SIT5 group, $n = 30$), and those who had an indication for SIT (IgE-dependent persistent asthma caused by sensitization to HDMs) but did not received SIT because of lack of have parental or patient consent (control group, $n = 30$). On the basis of the data from medical records, all patients had a history of at least 2 years of regular asthma symptoms requiring long-term treatment with inhaled corticosteroids (ICSs) at a minimal dose necessary to control asthma between 400 and 800 μg of budesonide before SIT (for the SIT3 and SIT5 groups) or before entering the study (for the control group). Patients and their parents were required to demonstrate understanding of the diary used to record daily symptoms. Patients were also required to be able to perform reproducible spirometry, exhibiting a resting forced expiratory value in 1 second (FEV_1) of at least 70%, and to have no contraindications for SIT.

Study design

This is a 3-year natural history study of 90 asthmatic children who sensitive only to HDM. During the prospective phase of the study, 3 groups were recruited (the SIT3, SIT5, and control groups). Data on the steroid-sparing effect during immunotherapy for the SIT3 and SIT5 groups and in the respective period for the control group were analyzed retrospectively (the retrospective phase of the study). The flowchart of the study is presented in Figure 1.

Patients from the outpatient population of our allergy clinic center who had indication for SIT were desensitized (the retrospective phase of the study). The decision of whether patient received 3 or 5 years of SIT was made in the retrospective phase of the study and was individualized to each patient, reflecting real-life circumstances and current recommendations. Patients from the SIT3 and SIT5 groups were desensitized according to manufacturer's recommendation. The extracts (Phostal; Stallergens, Antony, France) were administered subcutaneously at weekly intervals for approximately 3 months, according to a standard dose schedule. Increasing doses of HDM extract (build-up phase) were administered up to

a maintenance dose of 0.8 mL (1,000 STU), which corresponds to 5.9 μg of major allergens. This dose was continued monthly for 3 or 5 years (maintenance phase). Avoidance measures were recommended to all patients before immunotherapy and were continued throughout the study. All children remained in the same environment during the study.

Patients attended an enrollment visit in 2007 and 3 annual follow-up visits at the clinic. During the prestudy visit, at the start of the prospective phase of the study (after SIT and in the respective period for the control group), all participants were informed of the purpose of the study and were told how to score asthma symptoms (daytime symptoms, incidents of nocturnal awakening, and the number of puffs of as-needed β_2 -agonist) and how to respond to the Paediatric Asthma Quality of Life Questionnaire (PAQLQ).⁹ A minimal daily dose of ICS capable of maintaining asthma control was recorded from the medical history. The first, second, and third visit were planned in the 3 consecutive years (2008–2010) at the end of the heating season (maximum natural exposure to HDM: September to March).¹⁰ During each study visit clinical symptoms were assessed, lung function was measured, and ICS dose and the patients' asthma diaries and PAQLQ responses were evaluated in all patients. In addition, at the third visit methacholine challenge and skin prick tests were performed.

Asthma control was assessed via each patient's diary card¹¹ and PAQLQ, lung function measurements,¹² the analysis of the reduction in a required ICS dose, asthma remission, and methacholine challenge.¹³ A diary card and PAQLQ were completed during the period between September and March. The mean asthma symptom score was calculated for this period.

Diary card

The daily diary card included daytime symptoms (completed at bedtime), incidents of nocturnal awakening (recorded in the morning on awakening), and the number of puffs of as-needed β_2 -agonist. The daytime asthma symptoms and nocturnal awakenings were scored subjectively as follows: 0, no symptoms during the day

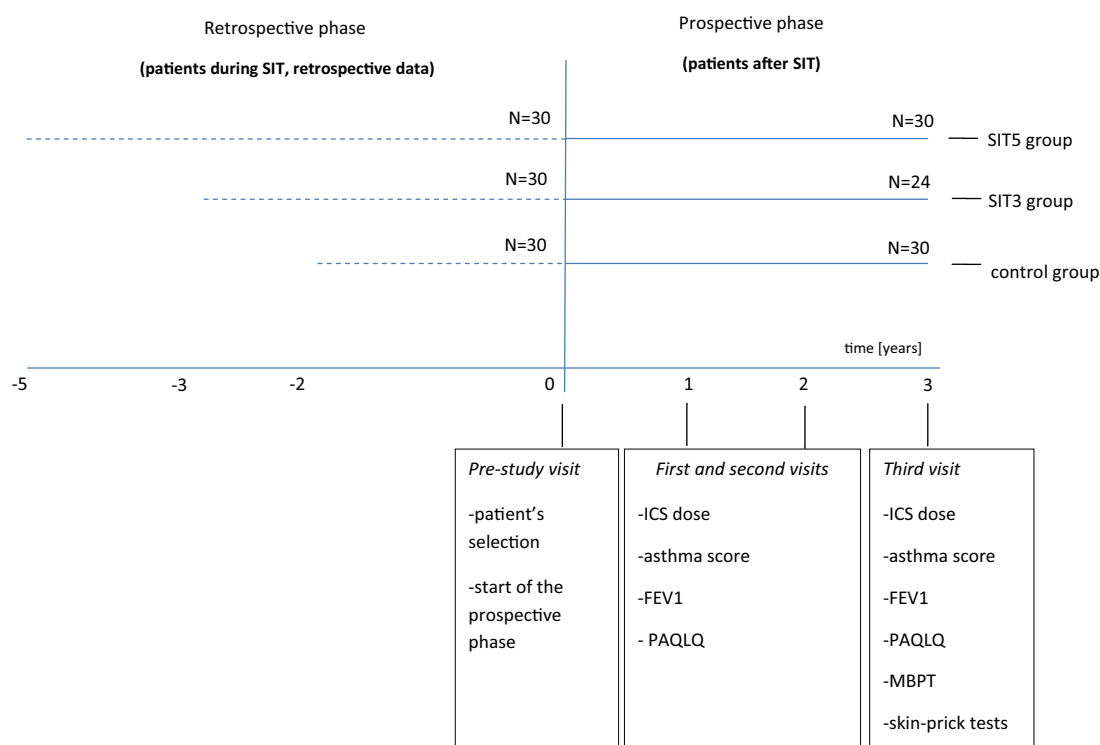


Fig. 1. Flowchart of the study.

or night; 1, symptoms that did not affect any activities during the day or night; 2, symptoms that affected at least one daily activity or disturbed the night; and 3, symptoms that affected 2 or more daily activities or sleep disturbances throughout all night or most of the night. The use of β_2 -agonists was scored as follows: 0, none; 1, once a day; 2, 2 to 3 times a day; and 3, more than 3 times a day. The minimum score for each day was 0 (no symptoms during the daytime, no symptoms at night, and no use of β_2 -agonists). The maximum score was 9 (severe symptoms during the day and night and the use of the β_2 -agonists >3 times a day).

Paediatric asthma quality of life questionnaire

Health-related quality of life was assessed by the Polish version of the PAQLQ by Juniper software (Juniper Networks, Sunnyvale, California).⁹

Principles for reducing the ICS dose

The minimal daily dose of ICS capable of maintaining asthma control was calculated according to guidelines¹⁴ before and after the retrospective phase and during the prospective phase of the study (3 consecutive years); only the September through March (the season with the maximum levels of natural exposure to HDM)⁹ periods were included. Each time, ICS doses were converted into the budesonide doses. Reduction in the minimal daily dose of ICS was calculated according to the following rule: (ICS dose after SIT – ICS dose before SIT)/ICS dose before SIT $\times$ 100%.

Skin prick testing

Skin prick testing (SPT) was performed with the inhalant allergens *D. farinae*, *D. pteronyssinus*, *Alternaria*, *Cladosporium*, cat dander, dog dander, mixed grass pollen, rye, birch, hazel, ribwort, alder, and *Artemisia vulgaris* together with a positive (histamine chloride, 10 mg/mL) and negative (glycerol) control (extracts from Allergopharma-Nexter, Reinbek, Germany). A positive SPT reaction was defined as a mean wheal diameter greater than 3 mm in excess of the negative control.

Methacholine bronchial provocation test

A methacholine bronchial provocation test (MBPT) was performed using the dosimeter technique APS Pro (Erich Jaeger GmbH, Hochberg, Germany) with controlled tidal breathing. After the pulverization physiologic diluent, methacholine was delivered in 4 cumulative doses of 0.015, 0.045, 0.18, and 0.72 mg. A negative MBPT result was defined as a provocation dose that caused a decrease in forced expiratory volume of 1 second (FEV₁) of 20% (PD₂₀) greater than 0.72 mg. MBPT was continued with 2-min intervals between the inhalations until a decrease in FEV₁ of 20% or greater was obtained. PD₂₀ was calculated by linear interpolation on a log dose-response curve.

Asthma remission

Asthma remission was defined as the absence of any symptoms that required asthma medication for at least 12 months with a negative bronchial provocation test result.

Statistical analyses

The present study was designed to achieve at least 85% power (for 25 patients completing the study per treatment arm) in detecting a 15% difference between the SIT3 and SIT5 groups in the ICS dose reduction after the prospective phase of the study (the primary outcome). Calculations were performed for a 1-sided Mann-Whitney test based on the assumption that the variability and distribution of our primary outcome was similar to that observed in a previous study¹⁵ and also similar to our unpublished data on the steroid-sparing effect of SIT. An allowance was made for a 20% dropout rate. We compared the baseline characteristics of the patients using χ^2 tests for discrete variables and the 1-way analysis of variance for continuous variables. To determine differences within groups, the *t* test was used. To compare changes in the response to treatment between groups, analysis of variance with the Tukey-Kramer post hoc test was used. Variables that exhibited a heavily skewed distribution were compared within groups using Wilcoxon test and compared between groups using the Kruskal-Wallis test followed by post hoc comparisons with the Dunn test. *P* < .05 (2-tailed) was regarded as statistically significant.

This study was approved by the Medical Ethics Committee of the Medical University. All parents or guardians and children provided written consent for participation in the study.

Results

Patients

Eighty-four children completed the study; only 6 (7%) dropped out, all from the SIT5 group. In all cases, the reason for dropping out was lost to follow-up (family moved or family changed health care provider); 2 patients in the first year of the prospective phase and 4 patients during the second year. Baseline characteristics of the patients who completed the study are listed in Table 1. The minimal ICS dose controlling the symptoms at the beginning of the retrospective phase of the study was lower in the control group compared with both the SIT3 and SIT5 groups. No other differences were found between the study groups. At the end of the study, SPT revealed only one patient from control group with new sensitization. All study parameters at each study visit are presented in Table 2.

ICS dose reduction

The minimal controlling ICS dose reduction in the SIT5 group (median, 75%) was significantly higher compared with the SIT3 group (median, 50%) after immunotherapy discontinuation (first year of the prospective phase). At the end of the prospective phase, no differences were seen between the SIT5 and SIT3 groups (median, 100% and 94%, respectively). During the prospective phase the minimal ICS dose controlling the symptoms did not change in the control group and was significantly higher compared with the SIT5 and SIT3 groups. The results are presented in Figure 2.

Diary card

The mean asthma symptom score did not change during the prospective phase of the study within all groups; in the SIT3 and

Table 1
Baseline characteristics of the study participants

Characteristic	Control group (n = 30)	SIT3 group (n = 30)	SIT5 group (n = 24)	<i>P</i> value ^a
Age mean (SD), y	12.2 (2.9)	11.7 (3.8)	13.9 (3.7)	.07
Male, No. (%)	21 (70.0)	17 (56.7)	16 (66.7)	.54
FEV ₁ , mean (SD), % predicted	89.6 (10.4)	90.9 (11.2)	91.8 (10.6)	.75
Minimal ICS controlling dose at baseline, median (interquartile range), μ g/d	400 (200–400)	500 (400–600)	450 (400–600)	.01

Abbreviations: FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; SIT3, 3-year specific immunotherapy; SIT5, 5-year specific immunotherapy.

^aAnalyses of variance for age and FEV₁ Kruskal-Wallis test for minimal ICS controlling dose and χ^2 test for sex. All 3 groups were compared simultaneously.

Table 2Study end points at baseline (retrospective phase) and during the first, second, and third years of follow-up (prospective phase)^a

End point	First year of follow-up	Second year of follow-up	Third year of follow-up	ANOVA <i>P</i> value		
				Within group	Group vs control	Group vs SIT5/SIT3
SIT3 group						
Minimal ICS controlling dose, $\mu\text{g}/\text{d}$	200 (100–400)	200 (100–200)	50 (0–200)	<.001	.001	.62
Asthma symptom score	0 (0–0.2)	0 (0–0)	0 (0–0)	.94	<.001	.94
FEV ₁ , % predicted	89 (85–97)	91 (87–99)	92.5 (89–98)	.045	.76	.53
PAQLQ score	7 (6.6–7)	7 (6.6–7)	7 (6.7–7)	.56	.77	.89
SIT5 group						
Minimal ICS controlling dose, $\mu\text{g}/\text{d}$	150 (0–300)	200 (0–400)	0 (0–200)	<.001	<.001	.62
Asthma symptom score	0 (0–0.25)	0 (0–0.18)	0 (0–0.18)	.35	<.001	.94
FEV ₁ , % predicted	91 (84–102)	90 (87–100)	98 (91–103)	.005	.19	.53
PAQLQ score	7 (7–7)	7 (6.7–7)	7 (7–7)	.68	.51	.89
Control group						
Minimal ICS controlling dose, $\mu\text{g}/\text{d}$	400 (400–400)	400 (400–500)	400 (200–500)	.65		
Asthma symptom score	0.5 (0.3–0.9)	1.1 (0.6–1.8)	0.5 (0.2–0.9)	.45		
FEV ₁ , % predicted	89 (82–97)	88 (80–96)	91 (82–99)	.047		
PAQLQ score	6.5 (6.1–6.8)	6.45 (6–6.8)	6.6 (5.8–6.8)	.86		

Abbreviations: ANOVA, analysis of variance; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; PAQLQ, Paediatric Asthma Quality of Life Questionnaire; SIT3, 3-year specific immunotherapy; SIT5, 5-year specific immunotherapy.

^aComparison within and between groups was assessed by ANOVA. The baseline values for minimal ICS controlling dose in the SIT3, SIT5, and control groups were as follows: 500 (400–600), 450 (400–600), and 400 (200–400) $\mu\text{g}/\text{d}$, respectively. Data are presented as median (interquartile range).

SIT5 groups, it was significantly lower compared with the control group. No significant changes were found in the asthma symptom score between the SIT3 and SIT5 groups (Table 2).

PAQLQ score

The mean PAQLQ score did not change during the prospective phase of the study within all groups; in the SIT3 and SIT5 groups, it was significantly lower compared with the control group. No significant changes were found in PAQLQ score between the SIT3 and SIT5 groups (Table 2).

Lung function

Analysis of variance revealed significant changes in FEV₁ within all study groups during the prospective phase. Between-groups comparison revealed a significantly higher increase in FEV₁ in the SIT5 group at the end of the prospective phase compared with the other 2 groups; no other differences were found between the study groups (Table 2).

Bronchial provocation test

We found a higher percentage of a positive bronchial provocation test result in the control group (87%) compared with the SIT3 (23%) and SIT5 (26%) groups at the end of the prospective phase; no differences were found between the SIT3 and SIT5 groups. Median

values of PD₂₀ in the SIT3, SIT5, and control groups were 0.71, 0.70, and 0.26 mg, respectively.

Asthma remission

At the end of the prospective phase, we observed 50% of patients with asthma remission in the SIT3 group, 54.2% in the SIT5 group, and 3.3% in the control group.

Discussion

To our knowledge, this is the first trial that prospectively explores the long-term effect of different durations of SIT after its discontinuation. Current immunotherapy guidelines^{16,17} suggest that SIT should be discontinued on an individual basis; the usual duration ranges from 3 to 5 years. Data suggest that SIT administration is effective in the treatment of respiratory allergy, and its efficacy continues after treatment discontinuation.^{18,19} However, trials specifically designed to address the topic of optimal duration and changes in effectiveness after the discontinuation of SIT are still lacking. We aimed to assess the possible differences in effectiveness between 3 and 5 years of HDM SIT in asthmatic children.

In our study, ICS dose reduction after 5 years of SIT was 25% higher than in case of children desensitized for 3 years (Fig 2). However, this difference was no longer observed after the next 3 years of prospective observation. This finding suggests latency in clinical improvement during HDM SIT. It is possible that the long-term effectiveness of SIT depends mainly on the early induction of allergen-specific tolerance, which is probably persistent.^{1–3} On the basis of the design of the current study, without immunologic outcomes we could not verify this hypothesis. The hypothesis of the latency in the clinical improvement during SIT could be explained by the maturity process of the immune system in children and the lower frequency of infections as a main trigger of exacerbation. From the clinical point of view, our study suggests that we need more time to reach full improvement in asthma symptoms together with the ICS dose reduction.²⁰ These findings seem crucial in the context of adherence to long-term intervention.²¹

According to the international recommendations,²² parameters used to evaluate SIT efficacy are mainly clinical, for instance, the symptoms and medication scores. We also added the PAQLQ score to those factors. The evaluation of the SIT3 and SIT5 groups revealed a lower asthma symptoms score and a higher PAQLQ score compared with the control group. This difference was stable throughout the 3 years of prospective observation, which is in accordance

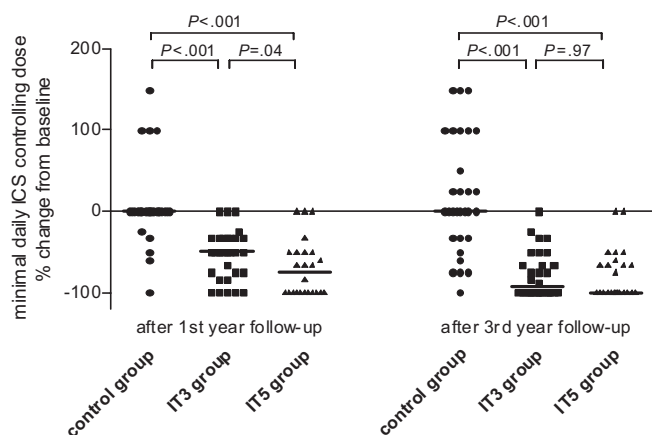


Fig. 2. Minimal daily inhaled corticosteroids controlling dose (percentage change from baseline) in all study groups.

with the previous studies on the long-term effect of SIT.^{23,24} Interestingly, a significant increase in FEV₁ within all the study groups during the prospective phase was observed. In addition, between-groups comparison revealed a higher FEV₁ in the SIT5 group at the end of the prospective phase compared with the other 2 groups. These findings suggest that among SIT5 patients, 2 additional years of SIT added a long-term clinical benefit to FEV₁. However, this difference, despite reaching a significant level, was under the minimum rate of 30% (over placebo) proposed by Malling²⁵ and was below the level of clinical perception.²⁶

Tabar et al⁷ recently published a study showing that the magnitude of the improvement observed among children after 3 years of SIT left too small a margin of benefit for the additional 2 years of SIT to make any difference. They concluded that 3 years of SIT is an adequate duration of the treatment of respiratory allergy caused by HDM. Our study, although similar, adds important information. First, we observed both the SIT3 and SIT5 groups prospectively for the 3 consecutive years, which allowed us to assess the changes in the reduction of the minimal ICS dose after the discontinuation of SIT and to observe latency in the clinical improvement after the 3-year course of SIT. Second, we included the control group, which made it possible to draw justifiable conclusions regarding the long-term effect of SIT.

We found a similar (50% of patients in the SIT3 group and 54.2% in the SIT5 group) percentage of asthma remission in both groups during our 3-year follow-up period after SIT discontinuation. Full clinical improvement during SIT defined as asthma remission was previously observed in a certain percentage of patients.⁴

Our study has some limitations. During data analysis, we observed that the minimal ICS dose controlling the symptoms was lower among the control group. This difference may be attributed to the fact that the control group consisted of children who did not agree to undergo SIT probably because of milder asthma symptoms. However, this fact did not influence the comparability observed between the SIT and the control groups. Another limitation includes the decision of whether the patient received 3 or 5 years of SIT. This decision was made in the retrospective phase of the study, without any control allocation (eg, randomization). It is possible that this approach could modify the results.

An adequate SIT treatment should guarantee clinical efficacy with a significant reduction of the ICS use and a long-term therapeutic benefit after its completion. In our study, these goals were achieved in both the SIT3 and SIT5 groups. Although the duration of SIT treatment should be recommended on an individual basis, we believe that 3 years of SIT is an adequate duration for the treatment of childhood asthma caused by HDM because 2 additional years of SIT added no disease duration benefit and only a possible benefit to FEV₁. An observation period longer than 3 years is needed to assess whether a 5-year course might be more effective.

References

- [1] Larché M, Akdis CA, Valenta R. Immunological mechanisms of allergen-specific immunotherapy. *Nat Rev Immunol*. 2006;6:761–771.
- [2] Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy. *J Allergy Clin Immunol*. 2007;119:780–791.

- [3] Matricardi PM, Kuna P, Panetta V, Wahn U, Narkus A. Subcutaneous immunotherapy and pharmacotherapy in seasonal allergic rhinitis: a comparison based on meta-analyses. *J Allergy Clin Immunol*. 2011;128:791–799.
- [4] Des Roches A, Paradis L, Knani J, et al. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract, V: duration of the efficacy of immunotherapy after its cessation. *Allergy*. 1996;51:430–433.
- [5] Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacqua G. Long-lasting effects of sublingual immunotherapy as add-on treatment in moderate persistent asthma due to birch pollen. *J Allergy Clin Immunol*. 2010;126:969–975.
- [6] Durham SR, Emminger W, Kapp A, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol*. 2012;129:717–772.
- [7] Tabar AI, Arroabarren E, Echechipia S, Garcia BE, Martin S, Alvarez-Puebla MJ. Three years of specific immunotherapy may be sufficient in house dust mite respiratory allergy. *J Allergy Clin Immunol*. 2011;127:57–63.
- [8] Stelmach I, Kaluzińska-Parzyszek I, Jerzynska J, Stelmach W, Majak P. Comparative effect of pre-seasonal and continuous grass sublingual immunotherapy in children. *Allergy*. 2012;67:312–320.
- [9] Stelmach I, Podlecka D, Majak P, et al. Validity of the Pediatric Asthma Quality of Life Questionnaire in Polish children. *Pediatr Allergy Immunol*. 2011;22:660–666.
- [10] Riccioni G, Di Stefano F, De Benedictis M, et al. Seasonal variability of non-specific bronchial responsiveness in asthmatic patients with allergy to house dust mites. *Allergy Asthma Proc*. 2001;22:5–9.
- [11] Stelmach I, Majak P, Jerzynska J, Kuna P. The effect of treatment with montelukast on in vitro interleukin-10 production of mononuclear cells of children with asthma. *Clin Exp Allergy*. 2005;35:213–220.
- [12] Stelmach I, Grzelewski T, Majak P, Jerzynska J, Stelmach W, Kuna P. Effect of different antiasthmatic treatments on exercise-induced bronchoconstriction in children with asthma. *J Allergy Clin Immunol*. 2008;121:383–389.
- [13] Miller MR, Hankinson J, Brusasco V, et al; ATS/ERS Task Force. Standardisation of spirometry. *Eur Respir J*. 2005;26:319–338.
- [14] Global Strategy for Asthma Management and Prevention. NIH publication 02-3659. Updated 2004 from the 2003 document. <http://www.ginasthma.org/Guidelineitem.asp?11=2&l2=1&intId=987>. Accessed November 25, 2009.
- [15] Blumberg G, Groes L, Haugaard L, Dahl R. Steroid-sparing effect of subcutaneous SQ-standardised specific immunotherapy in moderate and severe house dust mite allergic asthmatics. *Allergy*. 2006;61:843–848.
- [16] Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Allergen immunotherapy: a practice parameter second update. *J Allergy Clin Immunol*. 2007;120(suppl 3):S25–S85.
- [17] Alvarez-Cuesta E, Bousquet J, Canonica GW, Durham SR, Malling HJ, Valovirta E; EAACI, Immunotherapy Task Force. Standards for practical allergen-specific immunotherapy. *Allergy*. 2006;61(suppl 82):1–20.
- [18] Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of hymenoptera venom hypersensitivity: a meta-analysis. *Clin Ther*. 2000;22:351–358.
- [19] Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma. *Cochrane Database Syst Rev*. 2003;(4):CD001186.
- [20] Pham-Thi N, Scheinmann P, Fadel R, Combebas A, Andre C. Assessment of sublingual immunotherapy efficacy in children with house dust mite-induced allergic asthma optimally controlled by pharmacologic treatment and mite avoidance measures. *Pediatr Allergy Immunol*. 2007;18:47–57.
- [21] La Rosa M, Lionetti E, Leonardi S, et al. Specific immunotherapy in children: the evidence. *Int J Immunopathol Pharmacol*. 2011;24(4 suppl):69–78.
- [22] Canonica GW, Baena-Cagnani CE, Bousquet J, et al. Recommendations for standardization of clinical trials with allergen specific immunotherapy for respiratory allergy: a statement of a World Allergy Organization (WAO) task-force. *Allergy*. 2007;62:317–324.
- [23] Jacobsen L, Niggemann B, Dreborg S, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy*. 2007;62:943–948.
- [24] Eng PA, Borer-Reinhold M, Heijnen IA, Gnehm HP. Twelve-year follow-up after discontinuation of pre-seasonal grass pollen immunotherapy in childhood. *Allergy*. 2006;61:198–201.
- [25] Malling HJ. Immunotherapy as an effective tool in allergy treatment. *Allergy*. 1998;53:461–472.
- [26] Szefer SJ, Phillips BR, Martinez FD, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. *J Allergy Clin Immunol*. 2005;115:233–242.